DETAILED ACTION

Applicant's amendment filed 6/22/2011 have been received and entered into the present application.

As reflected by the attached, completed copy form PTO/SB/08A (one page total), the Examiner has considered the cited references.

Applicant's arguments filed 6/22/2011 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Status of Claims

Claims 1-2, 4 and 6-25 are currently under examination and the subject matter of the present Office Action.

Maintained Rejection:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner

to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4, 6-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (U.S. 6,383,471) in view of Li et al. (Am. J. Health-Syst. Pharm. 59, 539-44, 2002).

Chen et al. teaches an aqueous pharmaceutical composition include a hydrophobic therapeutic agent having at least one ionizable functional group and a carrier (abstract and column 34, line 66). The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers (abstract). Irinotecan is taught to be a hydrophobic therapeutic agent (claim 11). Acetic and ascorbic acid are taught as an ionizing agents to deprotonate the acidic functional group (column 11, lines 21-22). Hydroxypropyl cyclodextrin is taught to be a solubilizer (claim 52). Sodium acetate is taught to be a carrier (Table 20). Propylene glycol is taught to be a surfactant (column 2, lines 7-8).

Chen et al. is silent on an injectable solution having a pH of 2 to 5.

Li et al. teaches an intravenous injectable aqueous pharmaceutical composition comprising irinotecan and phosphoric acid (abstract). Camptothecins, such as irinotecan, are known for their anti-tumor activity (page 539, column 1). Hydrolysis of irinotecan is highly pH dependent with the lowest degradation rate observed in vehicles with a pH of less than 6. Irinotecan should be at a pH of less than 6 (page 541, column 3). The use of a vehicle with a lower pH should help to ensure that a higher concentration of the agent is delivered to the systemic circulation during an infusion (page 543, column 2, last paragraph).

One of ordinary skill in the art would have found it prima facie obvious at the time of the invention to administer the composition as an injection and to maintain a lower pH. One would have been motivated to do so because an aqueous pharmaceutical composition comprising irinotecan is known to be administered via route of injection and further it is known that a lower pH allows for the delivery of a higher concentration of irinotecan in the systemic circulation during infusion.

Additionally, it would have been obvious to vary the amount of different components and ratio between those different components as well as schedule of administration factors that would have been taken into consideration when making such a determination would have included, but not have been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosing regimen that would have actually been employed would have expected to vary widely and, in the absence of evidence to the contrary, would have not been inconsistent with that which is presently claimed.

Furthermore, the determination of the optimum pH of the claimed liquid dosage form would also have been a matter well within the purview of the skilled artisan. Such a determination would also have been made in accordance with a variety of factors, such as modifying the pharmaceutical carriers used to formulate the dosage form to optimize palatability of the dosage form and to maximize tolerability of the composition. In addition, the skilled artisan would also have been motivated to optimize the pH of the solution in order to maintain the active pharmaceutical ingredients in their desired salt form without any degradation of the active ingredients that may occur due to a change in pH.

Response to Applicant's Remarks

Applicant alleges that Chen et al. does not describe ionizing agents for the therapeutic agents including irinotecan can also include a salt of these acids. This is not found persuasive. Chen et al. clearly describes the use of ascorbic acid and acetic acid. Though Applicant points out that irinotecan has a basic functional group, Chen et al. clearly states that ionizing agents that protonate the basic functional groups of the therapeutic agents are organic acids such as acetic acid and ascorbic acid (column 11, lines 36-44). It is not clear what "salt" of ascorbic and acetic acid, Applicant is referring. The independent

claim fails to recite the use of salts of ascorbic acid and acetic acid. Furhter it should be noted that Chen et al. teaches that salts of acetic acid and ascorbic acids are used (column 11, lines 20-23). Sodium acetate is taught to be a carrier (Table 20).

Applicant alleges that Table 20 describes 70 possible carrier compositions, wherein a specific carrier is selected depending upon the properties of a therapeutic agent. Specifically Applicant alleges that the examples drawn to itraconzole and tretinoin do not comprise acetic acid or sodium acetate. This is not found persuasive. Applicant appears to be of the persuasion that, because Chen et al disclose compounds in addition to the one instantly elected, this somehow constitutes a complete lack of teaching of the claimed compound and/or constitutes a teaching away from the instantly claimed compound. This is not persuasive. A preferred or exemplified embodiment does not constitute a teaching away from other embodiments disclosed within the four corners of the reference, including non-preferred embodiments. Applicant is reminded that the disclosure of a reference must be considered as expansively as is reasonably possible to determine the full scope of the disclosure and, as a result, is most certainly most limited to that which is preferred and/or exemplified. Thus, the fact that other compounds may be exemplified, claimed and/or preferred does not negate or direct the artisan away from the broader teaching of the reference, which expressly provides for, and, thus, clearly contemplates the use of, a compound of identical structure to those within the genus of compounds instantly claimed. A reference will constitute a teaching so long as the disclosure clearly describes and enables such an embodiment, which, in the present case, such description is clearly found in Chen et al. The fact that the reference may teach embodiments that differ from Applicant's own invention does not negate, or teach away from, the teachings of the reference as a whole and what the reference as a whole would have reasonably suggested to one having ordinary skill in the art at the time of the invention. With regard to Applicant's contention that itraconzole and tretinoin do not comprise acetic acid or sodium acetate, Applicant is guided to MPEP 2123[R-5] which states " 'The use of patents as references is not limited to what the patentees describe as

their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain.' In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments." As such, though the two examples mentioned by Applicant fail to recite the use of acetic acid or sodium acetate, the use of the agents need not be exemplified or preferred.

Applicant alleges that Chen et al. do not describe a carrier for a therapeutic agent having basic functional groups comprising acetic acid and sodium acetate and further fails to mention the use of surfactants and additional solubilizers to solubilize irinotecan. This is not found persuasive. As stated in Chen et al., "[t]able 20 contains examples of carrier formulations according to the present invention, using a wide variety of surfactants, surfactant mixture, solubilizers and other components. The desired amount of ionizable hydrophobic therapeutic agent is included in the carrier to produce a pharmaceutical composition (column 37, lines 61-66).

Applicant alleges that one of skill in the art would not reasonable expect that the same composition would have provided solubilization of a different therapeutic agent because the chemical arts are unpredictable. Further, Applicant alleges that Li et al. suggest that the use of a phosphate buffer for adjusting the pH of an already solubilized irinotecan hydrochloride.

This is not found persuasive. Applicant's arguments are not commensurate in scope with the claims. The instant invention is not drawn to a method of solubilization but rather the claims recite a composition. Specifically, the independent claim recites "an injectable aqueous solution having a pH from 2 to 5, the preparation comprising water and the following components (A) and (B): (A) 7-ethyl-10-piperidinocarbonyloxycamptothecin and (B) acetic acid and sodium acetate as the components that

solubilize 7-ethyl-10-piperidinocarbonyloxycamptothecin in the aqueous solution of the acetic acid and sodium acetate at a pH of 2 to 5.

Applicant alleges that a typical aqueous solution for dissolving irinotecan is alkaline. As taught by Li et al. hydrolysis of irinotecan is highly pH dependent with the lowest degradation rate observed in vehicles with a pH of less than 6.

Applicant alleges that the specification supports that when an acid is different from that claimed it has inferior properties. According to Applicant, Li et al. uses a phosphate buffer which is different from the claimed acid. Applicant is reminded that phosphate buffer is not an acid, and as such one would not expect "inferior properties"

Applicant alleges that Li et al. describes the use of 20 ug/ml of irinotecan whereas the instant invention is drawn to 1-50 mg/ml of irinotecan. As stated in the rejection, it would be obvious to vary the amounts, and factors that would have been taken into consideration when making such a determination would have included, but not have been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosing regimen that would have actually been employed would have expected to vary widely and, in the absence of evidence to the contrary, would have not been inconsistent with that which is presently claimed.

CONCLUSION

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 7am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Brandon J Fetterolf/
Supervisory Patent Examiner, Art Unit 1628